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Treatment of Endodermal Sinus Tumor in Children Using a Regimen That Lacks Bleomycin

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Background: The EPO-VAC protocol was initiated to study 1) the efficacy of adding a cisplatin regimen (EPO) to VAC alone (the previous standard of care) and 2) the effect of replacing bleomycin with etoposide in the treatment of pediatric endodermal sinus tumors.

Methods: The eligibility requirements for entry included age <21 years at diagnosis, diagnosis of a primary gonadal or extragonadal tumor (excluding central nervous system tumors and stage I testicular tumors), and histological confirmation of endodermal sinus tumor. Children who met the eligibility criteria were treated with four courses of EPO (etoposide, cisplatin, vincristine) alternating with three courses of VAC (vincristine, dactinomycin, and cyclophosphamide).

Results: Eleven children were entered on the protocol. Six patients had extragonadal disease, five patients had ovarian primaries. Seven patients had low-stage tumor (I or II) and four had advanced-stage tumor (III or IV). Three of six evaluable patients attained a complete response at 21 weeks. The three patients with a residual soft tissue mass at restaging underwent further therapy. No patient has relapsed after a median of 51 (range 14–88) months of follow-up.

Conclusions: The results of this protocol suggests that a cisplatin-containing regimen that lacks bleomycin is active in childhood endodermal sinus tumors.

Key words: endodermal sinus tumor, germ cell tumor, cisplatin, children

INTRODUCTION

The use of chemotherapy to treat pediatric germ cell tumors has improved survival. In the era prior to the use of chemotherapy, fewer than 10% of children with malignant germ cell tumors survived [1]. The first combination chemotherapy found to be effective in patients with germ cell tumors was vincristine, ds, and cytoxan (VAC). VAC increased the survival rate to greater than 50% among patients with low-stage gonadal tumors but survival remained poor among those with advanced disease or extragonadal primaries [2–4]. Once the efficacy of the "Einhorn regimen" (cis-platinum, bleomycin, and vinblastine) was demonstrated for adults with germ cell tumors [5], most pediatric germ cell regimens were modified to include cisplatin as well. Currently, the majority of pediatric regimens which have incorporated cisplatin report over 70% survival, even in the most advanced stages of disease [6–11].

The underlying rationale for this protocol was twofold: 1) to alternate VAC with a modified Einhorn regimen based on the observation that the rotating administration of noncross-resistant chemotherapeutic regimens had been shown to decrease the emergence of drug-resistant strains of tumor and to enhance the likelihood of cure for certain tumors [12] and 2) to eliminate bleomycin to avoid the associated pulmonary toxicity. (A pilot protocol that used a 6-week induction with platinum, vinblastine, and bleomycin [PVB] followed by 12 months of maintenance with VAC has been previously reported [7].) Currently, in the treatment of adult germ cell tumors, the necessity of bleomycin is a subject of much debate [13–17]. We discuss in this report the results of 11 children diagnosed over a 6-year period with a regimen that lacks bleomycin and alternates courses of EPO (etoposide, platinum, and vincristine) and VAC.

MATERIALS AND METHODS

Eligibility Criteria

Between 1987 and 1993, 11 patients with newly diagnosed germ cell tumors were entered onto the EPO-VAC protocol. Six patients were treated at Dana-Farber Cancer Institute (Boston), two patients at Strong Memorial Hospital (Rochester), and one patient each at Roswell Park

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Cancer Institute (Buffalo), Brown University (Providence), and Children's Hospital and Health Center (San Diego). Although all patients who were eligible were enrolled at the Dana-Farber Cancer Institute and Roswell Park Cancer Institute, the other institutions enrolled patients only when there were no other active national protocols available for treating germ cell tumor patients. The protocol was approved by the human subjects committee at each institution. To be eligible for entry, the patient had to meet the following criteria:

1. Less than 21 years of age at diagnosis.
2. Diagnosis of a primary malignant gonadal or extragonadal tumor. Primary central nervous system tumors and stage I testicular tumors were ineligible for the protocol.
3. Histological confirmation of endodermal sinus tumor, either pure or in combination with other germ cell tumor types, including teratoma, embryonal carcinoma, dysgerminoma, or choriocarcinoma.

Staging

Staging was determined by the following factors: the extent of the surgical resection, biopsy of adjacent lymph nodes, sampling of ascitic and peritoneal fluid when present, sampling of the contralateral ovary if ovarian primary, chest computerized tomography (CT), abdominal CT or magnetic resonance imaging (MRI), radionuclide bone scan, and bone marrow aspirate and biopsy. Staging was defined using the system of Brodeur et al. [1] for testicular and extragonadal tumors; FIGO staging was used for ovarian tumors [18] (Table I).

TABLE I. Staging of Pediatric Endodermal Sinus Tumors

Brodeur staging (for testicular and extragonadal primaries)
- Stage I
  Localized disease, completely resected, without microscopic disease in the resected margins of the tumor or in the regional lymph nodes.
- Stage II
  Microscopic residual disease, capsular invasion, or microscopic regional lymph node involvement.
- Stage III
  Gross residual disease, gross residual lymph node involvement (greater than 2 cm diameter), or cytologic evidence of tumor cells in ascites or pleural fluid.
- Stage IV
  Disseminated disease involving lungs, liver, brain, bone, distant lymph nodes, and/or other sites.

F.I.G.O. staging (for ovarian primaries)
- Stage I
  Tumor limited to the ovary.
- Stage II
  Tumor extension and/or metastases to structures within the pelvis such as the uterus and/or fallopian tubes. No malignant cells found in ascitic fluid.
- Stage III
  Tumor extension within the abdomen, outside the pelvis, including positive ascitic fluid cytology and/or positive retroperitoneal lymph nodes.
- Stage IV
  Distant metastases, including lung and liver.

Treatment

The treatment regimen is summarized in Table II. Complete surgical resection of the tumor was attempted at diagnosis, if feasible, in all patients. Otherwise, a diagnostic biopsy or debulking was performed and definitive surgery was postponed until after completion of the EPO-VAC protocol.

After surgery, patients were treated with 21 weeks of EPO-VAC chemotherapy. Patients initially received two courses of EPO followed by alternating courses of EPO and VAC, resulting in a total of seven cycles of chemotherapy: four of EPO and three of VAC (Table II).

After 21 weeks, the patient was restaged. This included a CT or MRI of the primary site, chest CT, radionuclide bone scan, tumor markers (alpha-fetoprotein [aFP] and beta-human chorionic gonadotropin [β-HCG] and bone marrow aspirate and biopsy (only if initially positive). No further therapy was given to patients with normal tumor markers and no evidence of residual disease on imaging studies. Patients with a residual mass underwent second-look surgery, even if tumor markers were normal.

TABLE II. Schedule of Chemotherapy*

Week	1	4	7	10	13	16	19
	E	E	V	E	V	E	V
	P	P	A	P	A	P	A
	O	O	C	O	C	O	C

*EPO schedule: E = etoposide 150 mg/m^2 IV on days 2–5; P = platinum 100 mg/m^2 IV over 4 hours on day 1; O = vincristine 2.0 mg/m^2 IV on days 1 and 8. VAC schedule: V = vincristine 2.0 mg/m^2 IV on day 1; A = dactinomycin 1.25 mg/m^2 on day 1; C = cyclophosphamide 750 mg/m^2 on day 1.

If either mature teratoma or fibrotic tissue was found at reoperation, no further therapy was given. However, patients with residual endodermal sinus tumor received an additional four courses of EPO-VAC chemotherapy.

After the completion of treatment, patients were evaluated every 2 months for the first year, every 4 months during the second year, every 6 months during the third and fourth years off therapy, and every 12 months thereafter. The patients' renal and auditory function were followed off therapy in addition to serial monitoring of tumor markers.

Responses at 21 weeks was defined as follows:

1. Complete response (CR)—no evidence of disease either clinically or on diagnostic imaging studies and normal tumor markers (duration of response at least 1 month).

TABLE III. Patient Characteristics and Response to Therapy

Case	Sex	Years	Site	Stage	Response	Months since diagnosis	Comments on therapy
1	F	1	SCT[a]	I	NE[b]	88	
2	F	2	SCT	I	NE[b]	57	
3	F	1	SCT	III	NE[c]	14	Patient only received two doses of EPO and then VAC alone for 1 year.
4	F	1	SCT	IV	PR	62	Viable tumor adherent to coccyx at second-look surgery. Received four more courses of EPO-VAC
5	F	10/12	SCT	IV	CR	79	
6	F	1	Orbit	II	PR	40	Had stereotactic XRT to orbit after completion of 21 weeks of EPO-VAC
7	F	13	Ovary	II	NE[b]	57	
8	F	15	Ovary	III	NE[d]	51	
9	F	10	Ovary	II	CR	68	
10	F	18	Ovary	I	NE[b]	35	
11	F	12	Ovary	I	NE[b]	9	

[a]SCT = sacroccygeal tumor.
[b]NE = not evaluable due to complete resection at time of initial surgery.
[c]NE = not evaluable due to withdrawal from protocol after third course of chemotherapy.
[d]NE = not evaluable due to partial resection with microscopic residual at time of initial surgery.

2. Partial response (PR)—more than 50% decrease in the sum of the product of the perpendicular measurements of all evaluable lesions, without evidence of growth of tumor at new sites, lasting for 1 or more months and declining tumor markers.
3. No response (NR)—less than a 50% decrease or greater than a 25% increase in the sum of the products of the maximum diameter of measurable tumor or increasing levels of tumor markers.

RESULTS

Patient Characteristics

The characteristics of the patients are summarized in Table III. The distribution of the age of the patients at diagnosis was bimodal. The six patients with extragonadal tumors (sacrococcygeal and retro-orbital) were less than 2.5 years at diagnosis. The five patients diagnosed with ovarian tumors were adolescent: ages 10–18. All 11 patients treated on protocol were female. Every patient had an elevated aFP at diagnosis. Four patients were stage I at diagnosis, three patients were stage II, two patients were stage III, and two patients were stage IV. The sites of metastatic disease at diagnosis included the lung (two), bone (one), abdominal cavity (four), and ascitic fluid (two).

Response

The response data are summarized in Table I. Four patients were evaluable for response; seven patients were unevaluable due either to a complete resection (five) or a partial resection with microscopic residual (one) or withdrawal from protocol after severe infections following the first two courses of EPO (one).

Two of the four evaluable patients had a CR to 21 weeks of EPO-VAC. The other two patients had normal tumor markers but a residual soft tissue mass at the end of seven courses of EPO-VAC. One patient (patient 4) had a sacrococcygeal tumor that was unresectable at diagnosis so only a biopsy was done, leaving the coccyx intact. At second-look surgery, patient 4 had a soft tissue mass adherent to the coccyx that contained areas of endodermal sinus tumor; an additional four courses of chemotherapy were given after the resection. The other patient (patient 8) who had a PR to EPO-VAC had a retro-orbital primary. At the end of 21 weeks of EPO-VAC, the patient had normal tumor markers but a small residual mass adjacent to the optic nerve. Because of concern that second-look surgery might damage the optic nerve, and because of the possibility of intra-CNS extension along the optic nerve, stereotactic radiotherapy was given (4,540 rad) but no further chemotherapy.

All 11 patients remain disease free. Median follow-up is 51 months.

Alterations to Protocol

Patient 3 received only two courses of EPO and then received VAC alone for 1 year. The EPO was discontinued because of the bacterial and fungal sepsis she incurred after the initial two courses of EPO. *Patient 8 had a* residual soft tissue mass adjacent to the optic nerve. Second-look surgery was not performed because of the possibility of injuring the optic nerve. The patient received stereotactic radiotherapy to the site.

Toxicity

All 11 patients had at least one episode of neutropenia (ANC < 500); 9 patients had grade 4 neutropenia on more than one occasion. Severe neutropenia was more common following EPO than VAC. Hematopoietic growth factors were not used in this protocol and their incorporation could possibly ameliorate this toxicity.

Eight patients required hospitalization for fever while neutropenic; three patients were found to have bacterial sepsis, one of whom also developed fungal sepsis after the second course of EPO. None of the patients became hypotensive during an episode of sepsis.

Two patients had detectable hearing loss. The first patient had a 20–40 decibel (dB) loss at >4 kilohertz (KHz). This occurred after the second course of EPO. She received carboplatin rather than cisplatin for her third course of EPO, then was switched back to cisplatin for her final dose of EPO. The hearing loss did not progress. The second patient had a greater than 40 dB hearing loss at >2 KHz after the third course of cisplatin, so the final dose of cisplatin was not given.

No patient had an elevation of creatinine outside of the normal range; however, the creatinine on one patient doubled from baseline (0.3–0.7). Creatinine clearance remained above 60 ml/1.73 m^2 in the adolescent patients. Creatinine clearances were not routinely obtained on the infant patients; the newer isotope methods were not available at the time of treatment for the infants on the study.

All four adolescent patients who had reached menarche at time of diagnosis have resumed regular menses. One patient had a small bowel obstruction requiring surgery due to adhesions following her oophorectomy.

DISCUSSION

The study was undertaken to investigate the efficacy of alternating two regimens (VAC and EPO). A second objective was to investigate the efficacy of a regimen that lacked bleomycin. Several caveats about this study exist. First of all, the patients do not comprise a series of all eligible patients at a single institution, but a convenience sample from several institutions although no selection bias is apparent to the investigators. Secondly, the protocol included both low and high-stage patients. The low-stage patients would be expected to have high probability of survival even with less intensive therapy. However, none of the patients have relapsed, including the high-stage patients. Since the majority of relapses occur during the first 2 years after cessation of therapy [11,15–17] and 10 of the patients are more than 2 years post-diagnosis, the apparent efficacy of the regimen is unlikely to be due to short follow-up.

In general, regimens which include VAC [3,8, 16,17,19] in addition to platinum appear to have results inferior to those that which are solely platinum based [9–11]. This decrease in efficacy may be due to decreased dose intensity of platinum when used in combination with other myelosuppressive drugs.

Chemotherapeutic regimens for nonseminomatous germ cell tumors based entirely on platinum all produce a survival rate of at least 70%. Pinkerton et al. [11] reported that 11 of 13 children with advanced endodermal sinus tumors who were treated with either PVB or BEP (bleomycin, etoposide, and cisplatin), using a minimum of four cycles, achieved and maintained a continuous complete remission. In England, where the primary therapy for advanced-stage endodermal sinus tumors was either PVB or BEP, Mann et al. [10] reported a 72% survival rate in patients with stage IV disease. The German data from MAKEI reported by Gobel et al. [9] show an 83% survival rate for the 37 patients treated on a protocol that included four cycles of PVB, second-look surgery, and an additional four cycles of VPIC (etoposide, ifosfamide, cisplatin). Because of the platinum-related ototoxicity, the Hospital for Sick Children in London substituted carboplatin for cisplatin. Eleven of 14 patients treated with JEB (carboplatin, etoposide, and bleomycin) are relapse free and 13 of 14 are overall survivors [20].

Of note, all pediatric regimens to date contain bleomycin. However, the necessity of bleomycin for adults being treated for germ cell tumors is the subject of much debate. Wozniak et al. [13] reported the results of a randomized clinical trial comparing PVB to VPV (vinblastine, platinum, etoposide). The difference in survival between the two arms was not statistically significant ($P = .19$), but survival on the PVB arm was slightly better than on the VPV arm (77% vs. 73%). The three other studies which have reported on the results of a regimen lacking bleomycin have compared a two-drug regimen to a three-drug regimen [14–16]. Results with the three-drug regimen have been superior, although P values have been marginally significant.

In our pilot trial of a new regimen for treating germ cell tumors, we chose to replace bleomycin with etoposide because of the reportedly higher incidence of fatal bleomycin pulmonary toxicity in children [6,19–21]. Although the regimen appears efficacious, because we simultaneously replaced bleomycin with etoposide and incorporated VAC, we cannot separate the individual contributions of etoposide vs. VAC. However, the collective experience of other researchers would suggest that VAC does not add and may in fact detract from efficacy. Therefore, we propose that the pilot data from this nonrandomized trial suggest that EPO is an effective regimen.

The current joint regimen of the Pediatric Oncology Group and the Children's Cancer Study Group is a PEB, comparing high-dose vs. low-dose cisplatin. This regimen was selected because of randomized data from adults showing improved survival for BEP compared to PVB

[17]. (The replacement of vinblastine with etoposide was of concern because of the risk of secondary leukemia due to etoposide. Recent data [22], however, suggest that the risk is low [0.37%] using etoposide at conventional doses [cumulative dose 2,000 mg/m^2 or less]. We propose that the next randomized clinical trial to consider in the treatment of pediatric germ cell tumors is to compare PEB to a regimen lacking bleomycin, such as platinum, etoposide, and vinblastine.

CONCLUSIONS

In summary, we report the treatment of 11 children with endodermal sinus tumor using EPO-VAC chemotherapy. Seven were low stage and four were high stage. Eight patients attained a CR at 21 weeks, three received further treatment (1 EPO-VAC, 1 XRT, 1 VAC alone for 1 year), and none have relapsed. Even though the number of patients is small, we conclude that the inclusion of VAC probably does not add to the efficacy of a platinum-based regimen and that bleomycin may not be necessary for the successful treatment of pediatric germ cell tumors.

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